UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: May 3, 2013

TXR No.: 0056640

SUBJECT: **Fenpropidin:** Summary of Hazard and Science Policy Council (HASPOC) Meetings of April 11, 2013: Recommendations on the Requirement of the Acute Neurotoxicity Study.

PC Code: 012305
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0056640
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: import tolerance
Case No.: N/A
CAS No.: 67306-00-7
40 CFR: N/A

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THROUGH: Jess Rowland, Co-Chair
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TO: Linda Taylor, Ph.D.
Michael Metzger, Branch Chief
Risk Assessment Branches V & VII
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MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jeff Evans, Jeff Dawson, Jess Rowland, John Kough, Jonathan Chen, Mike Metzger, P.V. Shah, Ray Kent

Presenter: Linda Taylor

Other Attendees: Julie Van Alstine, Kristin Rury, Anwar, Dunbar, Danette Drew, Jaime D' Agostino

I. PURPOSE OF MEETING:

Risk Assessment Branch V/VII (RAB V/VII) is preparing a risk assessment for an import tolerance for fenpropidin on bananas. Fenpropidin is an unclassified fungicide that inhibits ergosterol biosynthesis in fungi. Currently, there are no tolerances in the U.S. However, because the proposed use on banana includes uses in countries that are major exporters of bananas to the United States, Syngenta Crop Protection proposed the establishment of a permanent tolerance for residues of fenpropidin *per se*. Based on the current 40 CFR Part 158 data requirements, an acute neurotoxicity study is required for fenpropidin. The Hazard and Science Policy Council (HASPOC) met on April 11, 2013 to discuss the need for an acute neurotoxicity study to support the import tolerance of fenpropidin, and also to address the lack of an endpoint for the acute-term oral exposure of children.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT:

Fenpropidin (1-[3-[4-(1,1-dimethylethyl)phenyl]-2-methylpropyl]piperidine) is an unclassified fungicide used in/on bananas that inhibits ergosterol biosynthesis in fungi.

The only source of human exposure to fenpropidin is *via* residues in imported food (bananas). Because fenpropidin is not an active ingredient in any product registered in the United States, occupational, residential, drinking water, and aggregate exposure are not expected to occur and were not included in the risk assessment.

In the most recent risk assessment (K. Farwell. D365475, 5/27/2009), endpoints were selected for chronic dietary human health risk assessments only. No hazard was identified for acute exposures *via* the oral route. An acute point of departure (POD) was not selected for the general population or for females 13+ because no appropriate endpoint attributable to a single exposure (dose) was identified from oral toxicity studies available, which included two developmental toxicity studies in rats.

A chronic Reference Dose (RfD) of 0.0023 mg/kg/day was derived from a NOAEL of 2.3 mg/kg/day established in a combined chronic toxicity/carcinogenicity study in rats and an Uncertainty Factor of 1000 which included 10x inter-species extrapolation, 10x intra-species variation and 10x data base uncertainty factor for the lack of a pre-natal developmental toxicity study in rabbits. The endpoint of concern is decreased body weight and body weight gain at 11.8 mg/kg/day (LOAEL).

III. TOXICITY PROFILE

Fenpropidin is categorized as having low acute (lethality) toxicity *via* the oral route of exposure (LD_{50} = males 2.17 g/kg/females 1.45 g/kg; Toxicity Category III). Acute lethality inhalation

and dermal studies are not available. Eye and skin irritation and skin sensitization studies are also not available (import tolerance).

In oral (diet) subchronic and chronic rat studies, there were irritant effects on the esophagus and stomach and dermal lesions. Peripheral parts of the body, such as tail and ears, were often affected. The numerous tail lesions in rats and mice included increased incidence of missing tail, pustules, necrosis, and swollen, thickened, or scaly tails. The dermal lesions in rats may be due to a direct irritant effect from compound in the feed; however, there may also be systemic effects because skin lesions were also found in the dog capsule studies. In the chronic dog study, the following skin lesions were noted: hardened and inelastic footpads with hyperkeratosis; scale formation, acanthosis, and hyperkeratosis of the ear; reddening of the skin with acanthosis of the epidermis; and chronic inflammation of the inguinal skin and chronic inflammation of the axillary dermis. Esophageal lesions in rats and mice included hyperkeratosis, dilatation, and acanthosis. Forestomach lesions in rats and mice included hyperkeratosis, inflammatory cell infiltration, ulceration, and acanthosis. Vomiting and salivation occurred in the dog capsule studies.

There was no evidence of increased susceptibility in a 1981 pre-natal developmental toxicity study in rats. In another pre-natal developmental study in rats conducted in 1994, there was evidence for susceptibility. However, the concern for this was determined to be low because the increase in skeletal variation seen in the fetuses was not statistically significant when compared to controls and the dose that caused the developmental effects was close to the maternal LOAEL. Susceptibility could not be ascertained due to the lack of a pre-natal study in rabbits. There was no evidence of increased susceptibility in the two generation reproduction study.

Since the completion of the risk assessment, the agency has received and reviewed a pre-natal developmental toxicity study in rabbits. Preliminary review of this study indicate a concern for increased susceptibility in the young and a potential endpoint of concern and a POD for assessing acute dietary exposure for the Females 13-49.

Preliminary review of a recently submitted developmental neurotoxicity study indicate pup death, decreases in brain weight, and alterations in brain morphometrics at the highest dose tested (27 mg/kg/day) in the absence of maternal toxicity (MRID No. 48836501).

The chronic dietary (food only; refined assessment) exposure is <100% of the population adjusted dose (cPAD) for all population groups and is 6.4% of the cPAD for children 1-2 years old. Quantification of cancer risk not required since there is only a suggestive evidence of carcinogenic potential (Table 5.2 of the 2000 HED HHRA. D365475).

Fenpropidin was completely metabolized and excreted mostly in urine. The only major urinary metabolite was 2-methyl-2-[4-(2-methyl-3-piperidine-1yl-propyl)-phenyl]-propionic acid, which accounted for 46-79% of the dose. Fenpropidin was rapidly and nearly completely absorbed following oral exposure at 0.5 mg/kg, but was incompletely absorbed at 100 mg/kg in females. No bioaccumulation occurred. The main metabolite found in feces in females was sulfuric acid mono-{2-methyl-2-[4-(2-methyl-3-piperidine-1-yl-propyl)-phenyl]-propyl} ester, which accounted for 6-9% of the dose at 0.5 mg/kg and 27% at 100 mg/kg, although, as noted above, absorption appeared incomplete in females at this dose. This same compound was the main

biliary metabolite in females, accounting for 6% of the dose. In males, all identified metabolites in feces were less than 1.7% of the dose.

IV. STUDY WAIVER REQUESTS

a. Neurotoxicity Studies

Acute and subchronic neurotoxicity studies are required in the 2007 revised 40 CFR Part 158 Toxicology Data Requirements because they provide important scientific information on potential nervous system effects from pesticide exposure. These studies can provide data on a wide range of functional tests for evaluating neurotoxicity including sensory effects, neuromuscular effects, learning and memory and histopathology of the nervous system. There is a subchronic neurotoxicity study on fenpropidin, which shows paresis, decreased fore- and hind-limb grip strength, and demyelination of the spinal cord and nerves.

With respect to considering whether the acute neurotoxicity study should be required as part of the tolerance assessment, the HASPOC used a WOE approach:

- **Evidence for neurotoxicity in the fenpropidin database of toxicology studies:** Evidence of neurotoxicity was observed in the chronic toxicity study in dogs. Demyelination of the spinal cord was observed in 3 of the 4 male dogs in the high dose group (20 mg/kg/day). One male in this group developed paresis and body weight loss and was sacrificed on week 38. A more extensive demyelination was observed in this dog than in the other males in this group. Salivation was observed in the subchronic dog study. Cataracts were observed in all male and female dogs at 20 mg/kg/day and in the one female in the subchronic neurotoxicity study with demyelination in the spinal cord and nerves.

- **Evidence for neurotoxicity in the database of toxicology studies for other pesticides:** No data available on structurally related chemicals.

- **Risk assessment considerations: In the most recent risk assessment, an endpoint of concern** for assessing acute dietary risk assessment was not established due to the lack of an appropriate endpoint. However, preliminary reviews of recently submitted developmental toxicity study in rabbits and a DNT indicate that an endpoint of concern can be established for acute dietary risk assessment. The potential PODs from these studies are approximately 20 mg/kg/day (DNT) or 10 mg/kg/day (developmental rabbit). The POD used for the chronic dietary risk assessment (2.3 mg/kg/day) is based on decreased body weight/body weight gain in the rat chronic toxicity/carcinogenicity study at the LOAEL of 11.8 mg/kg/day.

V. HASPOC RECOMMENDATIONS:

The HASPOC, based on a WOE approach considering all the available hazard and exposure information for fenpropidin, concludes that an acute neurotoxicity study is not

required at this time. This conclusion is based on the following considerations: 1) low acute toxicity following a single exposure (acute LD50 1.45-2.17 g/kg; Toxicity Category III); 2) the a POD from the recently submitted developmental toxicity study or the DNT would address the concerns for developmental as well as neurotoxicity; and 3) an acute neurotoxicity study, tested at higher dose in order to elicit neurotoxic effects, will not provide a POD lower than those available form the studies cited above.

The HASPOC further recommended that the toxicology science advisory council (TOXSAC) review the recently submitted developmental toxicity study in rabbits and a DNT for the selection of an endpoint for acute dietary risk assessment.